PTC THERAPEUTICS
measured by moments

PTC THERAPEUTICS' APPROACH TO GENE THERAPY

Gene therapy holds tremendous promise for some of the most debilitating and intractable rare, genetic disorders. PTC is at the forefront of a new and transformative era of gene therapy, developing a targeted gene therapy platform to treat devastating rare disorders.

PROMISE OF GENE THERAPY

1. Genetic disorders arise when a defective or missing gene stops the body from producing a critical protein properly.[1]
   - Genes provide instructions for the body to make proteins. These are essential for the body to develop and function normally.[1]
   - 80% of rare diseases are based on genetic mutations.[2]
2. Gene therapy involves introducing a therapeutic gene into the body to replace or correct the defective gene.
3. Vectors carry the therapeutic gene into the cell by injection or intravenously. This is in-vivo gene therapy.
   - Viruses are effective and efficient vectors. The virus is first modified to stop it from causing disease.[1]
4. One-time therapy potential for a single dose to confer lifelong improvement instead of a lifetime of ongoing treatment.
5. History of gene therapy
   - 1989 – First human gene therapy trial[3]
   - 2012 – First gene therapy approved in EU[4]
   - 2017 – First gene therapy approved in US[5]

PTC AT THE FOREFRONT

1. PTC has an advanced gene therapy pipeline for central nervous system disorders.

Gene Therapy	Disease	Pre-Clinical	Phase I/II	Pre-Registration
PTC-AADC	AADC Deficiency			✓
PTC-FA	Friedreich's Ataxia (FA)		✓	
PTC-AS	Angelman Syndrome (AS)	✓		

2. Targeted micro-dosing applied directly to areas involved in the disorder. This allows for greater efficacy, durability, lower risk of immunogenicity off-target effect, and efficient and scalable manufacturing.
   - PTC-AADC micro dose versus systemic gene therapy dose: x1,000 – x10,000
3. New state-of-the-art gene therapy manufacturing facility to foster the development of best-in-class therapeutics.

Continued on reverse

These devastating, rare neurodevelopmental disorders have limited or no treatment options.

Gene therapy addresses their underlying genetic cause.

AADC DEFICIENCY CAUSES A PROFOUND NEUROLOGICAL AND DEVELOPMENTAL FAILURE AT A VERY YOUNG AGE.[6]

- A defect in the DDC gene causes insufficient AADC protein, critical for dopamine production.[6]
- The body needs dopamine to develop/function normally.[7,8]

FRIEDREICH'S ATAXIA CAN PROGRESSIVELY ROB PATIENTS OF THEIR ABILITY TO WALK, SPEAK, SEE AND HEAR.[9]

- A defect in the FXN gene causes loss of frataxin protein, critical for cell function.[10,11]

ANGELMAN SYNDROME IS CHARACTERIZED BY SEVERE INTELLECTUAL AND DEVELOPMENTAL DELAYS.[12]

- A missing maternal copy of the UBE3A gene causes insufficient ubiquitin protein ligase E3A, critical for normal development and function of CNS.[13]

1 U.S. Food & Drug Administration website. What is Gene Therapy? How Does it Work? Available at: https://www.fda.gov/consumers consumer-updates/what-gene-therapy-how-does-it-work Last accessed October 2019.

2 EURORDIS website. About Rare Diseases. Available at: https://www.eurordis.org/about-rare-diseases Last accessed October 2019

3 Edelstein ML et. Al Gene therapy clinical trials worldwide 1989-2004-an overview. *J Gene Med*. 2004 Jun;6(6):597-602.

4 European Medicines Agency Press Release (2012). European Medicines Agency recommends first gene therapy for approval. Available at: https://www.ema.europa.eu/en/news/european-medicines-agency-recommends-first-gene-therapy-approval Last accessed October 2019

5 U.S. Food & Drug Administration. News Release (2017). FDA approves novel gene therapy to treat patients with a rare form of inherited vision loss. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-novel-gene-therapy-treat-patients-rare-form-inherited-vision-loss Last accessed October 2019

6 Hwu WL et Al. Natural History of Aromatic L-Amino Acid Decarboxylase Deficiency in Taiwan, *JIMD* Rep. 2018;40:1-6.

7 The Genetic and Rare Disease Information Center (GARD) website. Available at: https://rarediseases.info.nih.gov/diseases/770/aromatic-l-amino-acid-decarboxylase-deficiency Last accessed October 2019

8 AADC Research Trust website. About AADC. Available at: https://www.aadcresearch.org/copy-of-board-of-directors-2 Last accessed October 2019

9 National Institute of Neurological Disorders and Stroke. Friedreich Ataxia Fact Sheet. Available at: https://www.ninds.nih.gov/Disorders/All-Disorders/Friedreichs-ataxia-Information-Page Last accessed October 2019

10 Koeppen AH, Friedreich's ataxia: Pathology, pathogenesis, and molecular genetics. *J Neurol Sci*. 2011 Apr 15; 303(1-2): 1–12. doi: 10.1016/j.jns.2011.01.010

11 Cook, A. and Giunti P. Friedreich's ataxia: clinical features, pathogenesis and management. *British Medical Bulletin* 2017: 1;124(1):19-30.

12 Wheeler AC, et al. Unmet clinical needs and burden in Angelman syndrome : a review of the literature. *Orphanet Journal of Rare Diseases*, 2017: 12.164 doi: 10.1186/s13023-017-0716-z.

13 National Library of Medicine Genetics Home Reference, UBE3A gene. Available at: https://ghr.nlm.nih.gov/gene/UBE3A Last accessed October 2019